

WO9915150

Publication Title:

INORGANIC-POLYMER COMPLEXES FOR THE CONTROLLED RELEASE OF COMPOUNDS INCLUDING MEDICINALS

Abstract:

Abstract of WO9915150

This invention relates generally to the production and use of inorganic-polymer complexes for the controlled release of compounds including medicinals. Advantageously, the inorganic used is calcium sulfate. Data supplied from the esp@cenet database - Worldwide c94

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/00, 9/36	A1	(11) International Publication Number: WO 99/15150 (43) International Publication Date: 1 April 1999 (01.04.99)
(21) International Application Number: PCT/US98/19528 (22) International Filing Date: 22 September 1998 (22.09.98) (30) Priority Data: 08/935,300 22 September 1997 (22.09.97) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 08/935,300 (CIP) Filed on 22 September 1997 (22.09.97) (71) Applicant (for all designated States except US): BUFORD BIOMEDICAL, INC. [US/US]; 20000 Fisher Avenue, Poolesville, MD 20837 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): ROYER, Garfield, P. [US/US]; 20858 Green Garden Road, Upperville, VA 20185 (US). (74) Agent: BYRNE, Thomas, E.; Nixon & Vanderhye P.C., 8th floor, 1100 North Glebe Road, Arlington, VA 22201-4714 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
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INORGANIC-POLYMER COMPLEXES FOR THE CONTROLLED RELEASE OF COMPOUNDS INCLUDING MEDICINALS

FIELD OF THE INVENTION

This invention relates generally to the production and use of inorganic-polymer complexes for the controlled release of compounds including medicinals.

BACKGROUND OF THE INVENTION

Systemic antibiotic treatment is often unsatisfactory in cases of osteomyelitis as well as infections in devitalized tissue, avascular scar tissue, and other areas with insufficient blood supply. Increasing blood levels of antibiotics can result in toxicity. For example, aminoglycosides can produce ototoxicity and nephrotoxicity. Another problem with long-term systemic treatment with antibiotics is the selection of drug-resistant mutants. In poorly vascularized areas, the infectious organism may encounter concentrations below the minimum lethal concentration which provides the opportunity for selection of a resistant form. Also, in large-animal veterinary practice, the cost of the antibiotic for systemic use can be an issue.

Antibiotic formulations of polymethylmethacrylate have been employed as antiseptic bone cement and as beads either free or attached to a wire which is used for percutaneous removal [H.W. Bucholz, et al, Chirurg, 43, 446 (1970)]. PMMA is not bio-erodible.

An alternative is plaster of Paris (POP) which has been used without matrix biopolymers or medicinal complexing agents as $\text{CaSO}_4 \cdot 1/2\text{H}_2\text{O}$ [D. Mackey, et al, Clin. Orthop., 167, 263 (1982); and G.W. Bowyer, et al, J. Trauma, 36, 331 (1994)]. Polymethylmethacrylate and POP have been compared with regard to release profiles. Release rates from POP tend to be very fast.

Both polymethylmethacrylate and POP can be used to produce dimensionally stable beads and other structures. The acrylate cements or beads are formed by mixing pre-formed polymethylmethacrylate polymer, methylmethacrylate monomer, and a free-radical initiator. An exothermic reaction ensues which results in matrix temperatures as high as 100 °C. Many antibiotics such as polymyxin and tetracycline are inactivated by

these conditions [G.J. Popham, et al, Orth. Rev., **20**, 331 (1991)]. As mentioned above, polymethylmethacrylate is biocompatible but not resorbable. Therefore, beads used to treat local infection must be retrieved by surgery which is accompanied by the risk of reinfection.

POP beads or pellets are resorbable but show inferior drug release profiles [G.W. Bowyer, et al, J. Trauma, **36**, 331 (1994)].

Compositions containing hyaluronic acid have been used for topical administration of pharmacological substances [F. Della Valle, et al, U.S. Patent 5,166,331 and U.S. Patent 4,736,024].

OBJECTS OF THE INVENTION

It is an object of the invention to provide a safe resorbable delivery system which enables controlled release of medicinals.

It is an object of the invention to provide a delivery system with controllable setting time.

It is a further object of the invention to provide a delivery system which is an injectable liquid which solidifies in a timely way once in place.

SUMMARY OF THE INVENTION

The subject invention relates to a delivery system comprising:

- a) an inorganic compound capable of undergoing hydration and/or crystalization,
- and
- b) a matrix polymer, and/or
- c) a complexing agent.

In another embodiment, the system comprises a complexing agent and a medicinal.

Included within the invention are methods of producing sustained release of a medicinal in a mammal by administering the system with a medicinal to a mammal. A still further embodiment of the invention is a method of diagnosing disease in a mammal by administering a radiopaque matrix to the mammal.

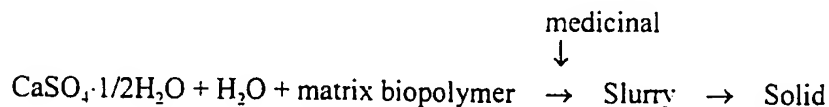
DETAILED DESCRIPTION OF THE INVENTION

The subject invention relates to a resorbable matrix with favorable release kinetics. Inorganic compounds such as $\text{CaSO}_4 \cdot 1/2 \text{H}_2\text{O}$ can be combined with biopolymer in the presence of a bioactive agent including medicinals to produce a matrix.

In addition to the inorganic compound there are:

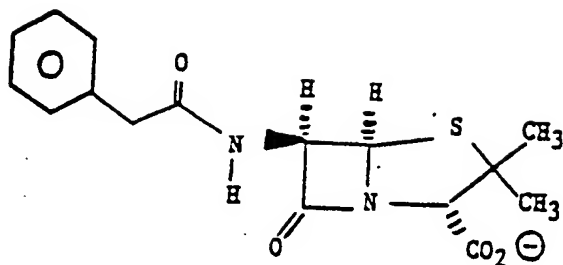
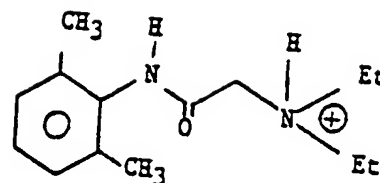
(i) a matrix polymer, and/or (ii) a complexing agent. As used herein, the term "matrix polymer" refers to a polymer (often a biopolymer) which serves to control the erosion rate, setting time, and influences the release profile by raising the viscosity of the medium in the pores and channels of the delivery system. As used herein, the term "complexing agent," refers to an agent (often a biopolymer), which is used to form a salt or conjugate with the active agent which in effect raises the molecular weight of the active agent and lowers its rate of efflux. The complexing agent is typically a small molecule capable of aggregation which has affinity for the active agent. Pharmacologically acceptable hydrophobic medicinal complexing agents include proteins such as albumin, lipids or cyclodextrins which can be used to complex neutral medicinal molecules or charged molecules which contain an apolar moiety. Liposomes containing a medicinal can be entrapped within the calcium sulfate matrix.

The reaction scheme for forming a matrix including a medicinal is shown below:



The consistency and viscosity of the slurry is dependent on the amount and nature of the matrix biopolymer. The slurry can be injected with subsequent formation of a solid in vivo.

A medicinal can exist in the inorganic-biopolymer complex either free or complexed to the medicinal complexing agent. The free compound is released relatively fast. The complexed medicinal is released relatively slowly often contingent on the bio-erosion of the inorganic-biopolymer complex. Antibiotics and local anesthetics are used to illustrate this principle:

 β -lactam antibiotic

Lidocaine

The resorbable inorganic-biopolymer complex can contain free antibiotic (e.g., as the sodium salt) or in the form of a biopolymer complex with a polycation such as a polypeptide such as polymyxin B or an aminoglycoside. Lidocaine is conveniently employed as the hydrochloride, the free base, or complexed as the salt of chondroitin sulfate or polyglutamate.

I. General considerations

The delivery system of the subject invention for use with medicinals must meet the following requirements:

1. Safety—non-toxic, non-immunogenic, non-pyrogenic, non-allergenic.
2. Resorbability—all components should be either assimilable or readily excreted.
3. Stability—the matrix should be sterilizable and precursors should have an acceptable shelf-life. Cast forms should be dimensionally stable.
4. Compatibility—the materials and the preparative conditions should not alter the chemistry or activity of the medicinal.
5. Programmability—the residence time and release profile should be adjustable.

There are typically two or three components in the inorganic-polymer complex matrix--

1. An inorganic compound, for example, $\text{CaSO}_4 \cdot 1/2\text{H}_2\text{O}$
2. Matrix polymer, for example, hyaluronic acid or dextran
3. Complexing agent, for example, chondroitin sulfate, cationic polypeptide, or cyclodextrin.

Inorganic Compounds

Calcium sulfate $\cdot 1/2\text{H}_2\text{O}$ (hemihydrate) is the preferred inorganic component. The hemihydrate takes up water and crystallizes as the higher hydrate. Unadulterated calcium sulfate matrix exhibits poor drug release profiles. With matrix polymers and complexing agent-active agent complexes the release profiles are improved. Other inorganics may be employed such as calcium silicates, aluminates, hydroxides and/or phosphates (see pages 72, 95, 327 in Reference Book of Inorganic Chemistry (1951) Latimer, W.H., and Hildebrand, J.M., Macmillan, New York, hereby incorporated by reference in its entirety).

The inorganic compound goes from slurry to solid in a reasonable time period, i.e., 10 minutes-two hours. The matrix biopolymer influences the setting time and the release profile. Sodium salts and chloride ion act as inhibitors. Sulfate salts and calcium salts accelerate the solidification process. Calcium pentosan polysulfate containing slurries solidify faster than those containing sodium as the counterion.

In an advantageous embodiment, the matrix has a porosity sufficient to permit the influx of cells (e.g., osteocytes). See Example 15.

Polymers

In order to slow the efflux of active agent, e.g., medicinal, from the dosage form, polymers, often biopolymers, are included in the matrix to raise the viscosity. Hyaluronic acid (e.g., 1-5%), proteins, e.g., collagen (gelatin), fibrinogen, which form viscous solutions (e.g., 1-30%), and dextran (e.g., 1-50%) are examples. Viscosity can be changed as a function of time. Hydrolytic enzymes such as a protease, can be included to lower the viscosity as a function of time to speed the efflux and compensate for the decrease in the medicinal gradient. This feature provides for a desirable release profile. For medicinal uses, biopolymers (polymers of biological origin) are advantageously employed.

Complexing Agents

To make biopolymer-medicinal complexes for use in parenteral matrices, polymers which are known to be safe are employed. Polymers useful for this purpose include, but are not limited to, the following:

- glycosaminoglycans such as chondroitin sulfate, hyaluronic acid
- polynucleotides
- acidic proteins
- polyglutamic acid
- polyaspartic acid
- pentosan polysulfate
- dextran sulfate

The polymers should be assimilable for use in veterinary or human medicine.

In another embodiment, lower molecular weight compounds can be used as the complexing agent. For example, carboxylic acids such as caprylic acid, undecylenic acid, piperacillin, penicillin V, nafcillin or cefazolin.

For the complexation of anionic medicinals such as some β -lactam antibiotics advantageous polymers include polypeptide cations such as polymyxins and aminoglycoside antibiotics such as amikacin. For medicinals not carrying a net positive or negative charge or those that possess a significant amount of apolar character, neutral complexing agents are employed. Examples include cyclodextrins, Polysorb 80 and proteins which bind the medicinals. Small molecules which aggregate and bind the medicinals are alternatives. Apolar molecules which form multi-molecular aggregates can be employed. This type is exemplified by liposomes. A series of active medicinals which possess varying degrees of apolar character can be advantageously employed with the apolar complexing agent. Such a series is exemplified by hydrocortisone hemisuccinate-sodium, hydrocortisone, hydrocortisone acetate, and hydrocortisone octanoate.

The rationale for using complexing agents is based on Stokes law:

$$D \propto 1/Mv$$

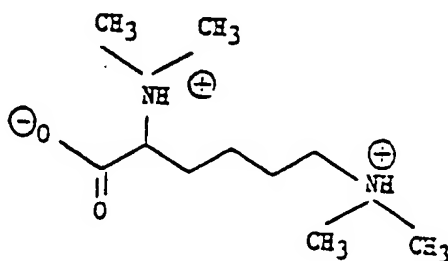
D = the diffusion coefficient

M = the molecular weight of the medicinal

v = the viscosity of the medium

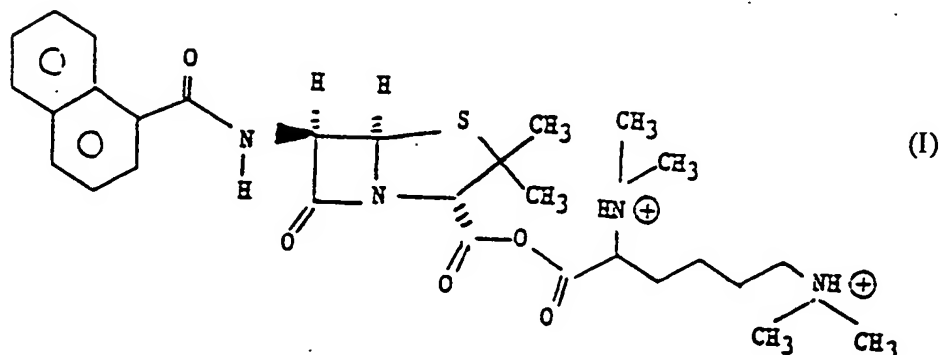
Use of complexation biopolymers in effect, raises the molecular weight of the medicinal. The presence of both the matrix biopolymer and medicinal complexing agent can increase the viscosity within the matrix which lowers the diffusivity. Another view of the retardation of release concerns the maintenance of electrical neutrality. In order for the charged medicinal to diffuse away from the medicinal complexing agent an external counterion must first diffuse into the matrix and exchange for the medicinal.

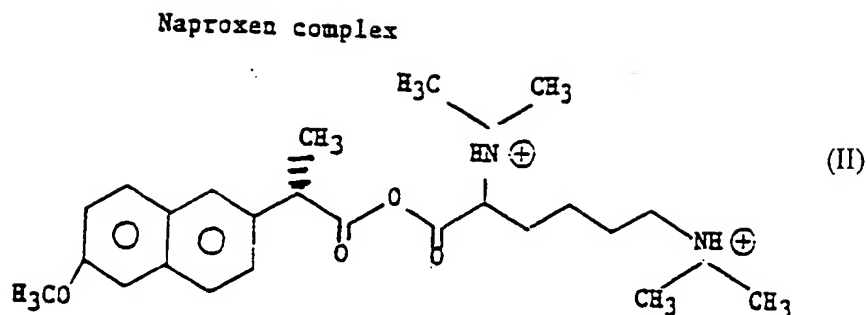
The medicinal complexing agent serves to delay the release of the medicinal. The medicinal complexing agents can be in the form of a cationic polymer such as polypeptide cations, aminoglycosides, an anionic polymer such as chondroitin sulfate and a neutral compound such as cyclodextrin or a lipid or mixture of lipids. Also, chondroitin sulfate and other polyanions can be used with a tetramethyl-lysine linker--



which is used in anhydride linkage with β -lactam antibiotics (I) or a carboxylated NSAID (II):

Nafcillin Complex





Use of a series of medicinal complexing agents of varying size is illustrated by the example of penicillin G ionically complexed to progressively larger amines: procaine, benzathine, polymyxin, and other polypeptide cations. Cationic medicinals may be analogously bound to progressively larger carboxylate (sulfate) containing compounds. An enzymatic digest of chondroitin sulfate constitutes a random series of sizes and is conveniently prepared.

In one embodiment of the invention, there is a complexing agent and a medicinal only (without an inorganic); see e.g., Table I compositions E, H, J, K, L and O. In another embodiment of the invention, there is a matrix polymer and a medicinal only (without an inorganic), for example, hyaluronic acid and a medicinal such as an antibiotic or anesthetic. Complexing agents for non-medicinals are discussed in section V "Non-medical Applications."

Advantageous delivery systems of the invention are shown in Table I below:

TABLE 1

Formulation	CaSO ₄ 1/2H ₂ O	Matrix polymer	Complexing agent	Medicinal
A R/100mgIa	1g	HA - 0.6 ml (2%)		50 mg NF
B R/100mgIa	1g	Dextran - 0.6ml(20%)	lecithin - 100mg	50 mg NF
C	1g	HA, 0.6 ml (2%)	polyglutamic acid	100 mg lidocaine
D	1g	HA, 0.6 ml (2%)	chon S	100mg amikacin
E	-	HA, 0.6 ml (2%)	chon S	Amikacin 100 mg
F	1g	Dextran - 6ml (20%) HA, 0.6 ml (2%)	polymyxin	Cef 100 mg
G	1g	HA, 0.6 ml (2%)		500 mg HC (10% a.i.)
H	-	HA, 0.6 ml (2%)		500 mg HC (10% a.i.)
I	1g	HA, 0.6 ml (2%)		50 mg cis-platin
J	-	HA, 0.6 ml (2%)	chon S	Lidocaine 100 mg
K	-	HA, 0.6 ml (2%)	chon S	Morphine 100 mg
L	-	HA, 0.6 ml (2%)	chon S	Hydromorphone 100 mg
M	1g	HA, 0.6 ml (2%)		50 mg Imip
N	1g	HA, 0.6 ml (2%)		5 mg BMP-2
O	-	HA, 0.6 ml (2%)	polymyxin	100 mg Imip
P	1g	-	0.6 ml chon S	lidocaine 24 mg
Q	.5g	HA, 1 ml (2%)		HA
R*	1g	Dextran 200 mg (solid)	-	Lidocaine 100 mg (solid)
S	1g	Gelatin (10%) 0.6 ml	-	Lidocaine 100 mg (solid)

R = radiopaque

Ia = iodipamide

HA = hyaluronic acid, sodium salt

NF = norfloxacin

Imip = imipenem

Cef = cefazolin

HC = hydrocortisone in CD

CD = 2-hydroxypropyl-(3-cyclodextrin)

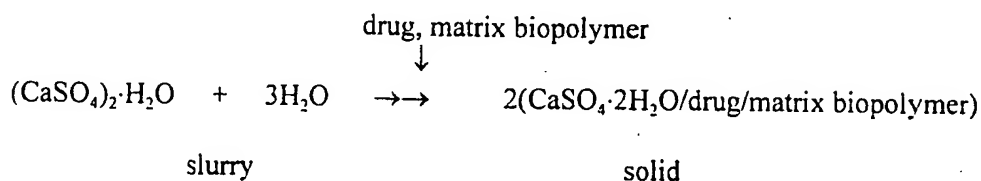
Chon S = chondroitin sulfate

LD = lidocaine

* Slurry is made with 0.6 ml of water.

II. Production of the Inorganic-Biopolymer Complex-Medicinal Matrix and Modes of Administration

The basis for formation of the inorganic-biopolymer complex matrix can be expressed in the following reaction:



The drug, free and complexed to a medicinal complexing agent, is conveniently mixed with calcium sulfate as a finely ground solid. The matrix biopolymer is included to influence the setting time and the drug release profile.

The setting time can be adjusted so that the user can administer the inorganic-biopolymer complex matrix in the form of a liquid using a syringe with a 23 gauge needle or larger. The matrix will solidify soon thereafter. It is convenient to transfer the slurry to the barrel of a syringe using a spatula or second syringe. The plunger is inserted and the inorganic-biopolymer complex matrix is injected after expulsion of air. Salts of fatty acids can be included to facilitate release from the mold, e.g., 1-3% calcium stearate. Subcutaneous injections are routinely done with a syringe fitted with a 25-gauge needle. Dispensing into molds can be accomplished using a syringe fitted with a blunt needle or in some cases a pipette. The liquid injection can be s.c., i.m., or i.p. Advantageously, the administration is done by parenteral injection.

Administration of the solid matrix can be by surgical implant, oral, i.p., i.a. or p.a. Specific sites can be targeted for administration of the medicinal such as an anesthetic or anti-inflammatory.

The drug is conveniently employed as a solid which can be finely ground and mixed with the calcium sulfate. The matrix polymer is routinely used as a solution. In a representative formulation the following proportions and ingredients are used:

<u>Ingredient</u>	<u>Amount</u>
Calcium sulfate	1 g
Drug	50 mg
matrix biopolymer at 2%	0.6 ml

If the calcium sulfate amount is set at 1g, the amount of drug used is in the range of 1-200mg and the matrix biopolymer in the range of 0.4-3ml. The concentration of the matrix biopolymer ranges from 0.1-50%.

Cooling of the ingredients prior to mixing slows the reaction. Increased liquid/solid ratios tend to slow the reaction also. Low molecular weight alcohols, such as propanol and butanol, significantly prolong the setting time. The influence of two matrix biopolymers is shown in Table 2.

Polyethylene glycols (PEGs) can be used to suspend medicinals and calcium sulfate. The solidification is retarded by PEG. Chloride and sodium salts also inhibit solidification. Availability of water also is used as a means to control the rate of solidification. Silver sulfadiazine cream solidifies underwater. The isopropanol diffuses out and water diffuses in where it reacts with calcium sulfate-hemihydrate which results in hardening. The resultant material then slowly releases the medicinal. See Example 11. Topical formulations permit selection of a complexing agent and/or matrix polymer of non-biological origin. Examples include polyethyleneglycol (PEG) and polyvinylpyrrolidone (PVP).

Table 2**Change of setting time by matrix biopolymers****A. Hyaluronic acid (HA)**

Calcium sulfate	HA (%)	Setting time (min)
1g	0.6ml (0)	75
1g	0.6ml (.2)	60
1g	0.6ml (2)	20

B. Dextran

Calcium sulfate	Dextran (%)	Setting time (min)
1g	0.6ml (0)	75
1g	0.6ml (10)	15
1g	0.6ml (20)	25
1g	0.6ml (50)	80

Dextran (clinical grade) is a convenient accelerator at low concentrations. The solutions are less viscous than HA solutions and dextran is inexpensive.

The inorganic-biopolymer complex can be formed as spheres, granules, cylinders, tablets and beads (including microbeads) for injection or for use in capsules. The latter can be formed by dispersing the slurry into a rapidly stirring water-immiscible medium. The size of the beads can be determined by the amount and nature of the surfactant and the stirring rate. Milling and sieving to produce beads (30-60 μ) is an alternative approach. For orthopedic and dental use the inorganic-biopolymer complex matrix can be molded and or carved into specific shapes to conform to voids in bone structures. Just prior to formation of the intractable solid, the material is plastic and can be conveniently shaped to fit openings of irregular geometry.

III. Release Profile

An idealized release profile has three phases. The burst phase is not necessary for many drugs but would be advantageous for anesthetics and antimicrobics. The maintenance, or zero-order phase, is a desirable result of the delayed release of the complexed drug. The drop-off, referred to as the closing phase, occurs as the bioerosion process comes to a conclusion. Sub-batches of beads of varying size, drug load, and release profile can be blended to provide the desired release profile.

With regard to control of the release profile, one should consider that the rate of diffusion is given by

$$\text{rate} = DA(d[m]/dx) \quad (1)$$

D = the diffusion coefficient

A = the surface area

d[m]/dx = the medicinal gradient

Also, according to Stokes Law

$$D \propto 1/Mv \quad (2)$$

D = diffusion coefficient

M = molecular weight

v = viscosity

The use of the medicinal complexing agent will change the effective molecular weight of the medicinal. The matrix density and composition will influence the internal viscosity of the delivery system.

Simultaneous use of medicinal complexing agents of varying size is used advantageously. For example, penicillin G in the form of salts of potassium, procaine, polymyxin, and aminoglycosides such as amikacin can be used. Polyanions with a range of sizes can be produced by enzymatically digesting glycosaminoglycans.

The shape of the delivery device will dictate the surface area. For example the surface area of a sphere is given by

$$A = 4 \pi r^2 \quad (3)$$

The volume of a sphere is given by

$$V = \frac{4\pi r^3}{3} \quad (4)$$

Combining (3) and (4) gives

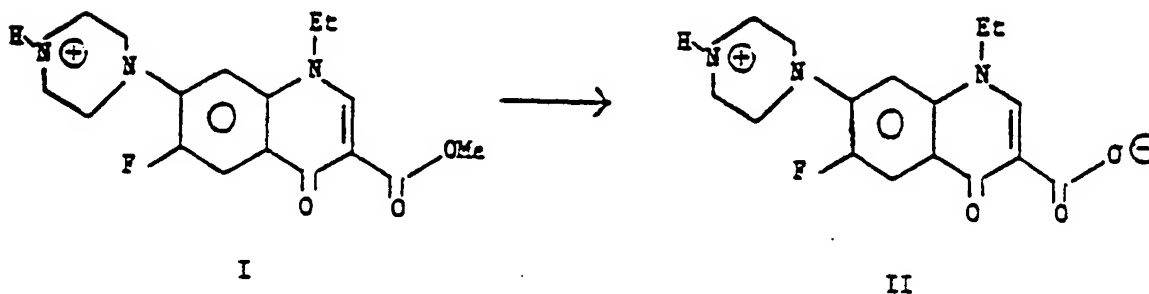
$$A/V = 3/r \quad (5)$$

According to equation (5) as beads get smaller, the surface area per a given volume of inorganic-biopolymer complex increases. One cc of inorganic-biopolymer complex matrix dispersed as small beads delivers drug faster than one cc dispersed as large beads. The desired zero-order release profile can be approached by using the proper blend of beads of varying size.

Residence time in vivo and bio-compatibility have been assessed using hamsters. Inorganic-biopolymer complex matrices were injected (0.3ml) subcutaneously. At timed intervals the animals were sacrificed to determine the residence time and the condition of the injection site as judged by histo/path analysis. All formulations were very well tolerated. The proportion of calcium sulfate or density was an important factor in residence time. Denser formulations lasted longer. Calcium sulfate/ HA (3/2) show a residence time of 35 days. Calcium sulfate/ HA (1/2) showed a residence time of 20 days. Spherical beads (3.2 mm in diameter) made of calcium sulfate/HA (1/1) lasted ten days. Beads containing silver benzoate lasted two weeks and were well tolerated with no toxicity to local tissues.

Another means to control the release profile involves drug precursors. As the precursor is converted to the native compound, its avidity (affinity) for the medicinal complexing agent decreases which in turn raises its diffusivity, thus creating a biphasic

release profile. As opposed to release of a molecule that is covalently linked to a polymer, this embodiment is dependent on a change in polarity. Consider the following:



Compound I is positively charged at physiological pH. It is strongly bound to chondroitin sulfate. As it hydrolyzes to form Compound II, the net charge becomes zero and as a consequence the release is accelerated. A biphasic release profile is the result when free II is included in the dosage form. The release profile can be controlled by the nature of the hydrolyzable group attached to the carboxyl group. The hydrolyzable group can be an ester, an anhydride or other labile functionalities.

IV. Medicinals

A. Non-protein Drugs

The delivery systems described herein are well suited for sustained release of: an analgesic, an anesthetic, an anti-addictive preparation (e.g., naltrexone), an anti-microbial, an antiseptic (e.g., silver ion, and silver sulfadiazine, calcium peroxide, calcium hypochlorite), an anticoagulant, an antineoplastic, an antidepressant, an anti-diabetic agent, an antihypertensive drug, an anti-inflammatory agent, an anti-nauseant, an anorexic, an antiulcer drug, a cardiovascular drug, a chondroprotective agent, a contraceptive, an

antihistamine, a diuretic, a hormone/antihormone, an immunosuppressive, a narcotic detoxification agent, a uricosuric agent, and a wound healing promoter.

A logical alternative to systemic treatment is to employ delivery systems for local release of antibiotics. In this case, levels much greater than the minimum lethal concentration can be achieved in the therapeutic compartment while blood levels remain low. Inorganic biopolymer complexes can be implanted as beads after surgical debridement or the matrix can be injected as a liquid with subsequent solidification.

The inorganic-biopolymer complexes containing antibiotics are especially useful in filling cavities in bone produced by osteomyelitis. Placement of antibiotic-inorganic-biopolymer complexes in the vicinity of infected bone or other tissue results in eradication of the micro-organism and permits aseptic healing accompanied by resorption of the inorganic-biopolymer complex. When treating bone lesions, bone morphogenic proteins can also be included to promote growth of new bone.

Inorganic biopolymer complexes are effective for treatment of other local infections, such as joint sepsis, surgical infections, wound infections, uterine infections, oral-dental-periodontal infections, vaginitis, and localized abscesses. Likely infectious agents include *Aeromonas*, *Capnocytophaga*, *Citrobacter*, *Clostridium*, *Edwardsiella*, *Eichenella*, *Enterobacter*, *Enterococcus*, *E. Coli*, *Fusobacterium*, *Hafnia*, *Kingella*, *Klebsiella*, *Moraxella*, *Morganella*, *Mycobacterium*, *Pasturella*, *Peptostreptococcus*, *Plesimonas*, *Proteus*, *Pseudomonas*, *Staphylococcus*, *Streptococcus*, and *Vibrio*.

An advantageous antimicrobial for treatment of localized infections has the following characteristics:

1. Cidal
2. Broad spectrum
3. Non-toxic to local tissues
4. Soluble and mobile, that is, readily crosses inflamed membranes.

Antimicrobials of special interest include gentamicin, clarithromycin, minocycline and lincomycin, amikacin, penicillin, cefazolin, ciprofloxacin, enrofloxacin, norfloxacin, silver sulfadiazine, imipenem, piperacillin, nafcillin, cephalixin, vancomycin, nystatin.

and amphotericin B or salts thereof. Salts of amikacin-piperacillin and amikacin-caprylic acid are useful in that they provide slower release. Further, amikacin acts synergistically with piperacillin and other β -lactams.

In high risk surgical procedures, the antibiotic inorganic-biopolymer complexes can be used prophylactically. In abdominal surgery antibiotic beads can be distributed to provide antibiotic coverage at critical points. Placing antibiotic beads under the incision is often advantageous.

Chondroprotective agents such as chondroitin sulfate, hyaluronic acid, pentosan polysulfate and dextran sulfate can also be used, optionally with an antiinfective.

Inorganic biopolymer complexes for local delivery of anti-inflammatory drugs hold great promise for treatment of osteoarthritis, degenerative joint disease, and other such afflictions. Neutral and charged forms are advantageously employed together. For example, free hydrocortisone and hydrocortisone succinate complexed to polymyxin is a useful combination. The anti-inflammatory inorganic-biopolymer complexes are placed adjacent to diseased joints, tendon sheaths, etc. Use can accompany arthroscopic procedures both as an injectable and as pre-formed implants. NSAIDs are also of interest including naproxen, and disalicylate. NSAIDs, e.g., analgesics such as aspirin, and other medicinals can be formulated in tablet or capsule form for oral administration.

Inorganic-biopolymer complexes for pain control are primarily based on free and complexed cationic anesthetics such as lidocaine, buvicaine, bupivacaine, chlorprocaine, procaine, etidocaine, prilocaine, dezocine, hydromorphone, etc. An advantageous medicinal complexing agent is chondroitin sulfate. Tablets or beads are especially useful following arthroscopic procedures. Implants are placed next to the joint capsule laterally and medially. Pain relief is provided for 3-5 days which obviates or greatly reduces systemic use of narcotics.

In conjunction with surgical and diagnostic procedures, analgesia and tranquilization can be provided by the use of a complex of chondroitin sulfate and two bio-active compounds - fentanyl and droperidol. The simultaneous use of free and bound forms of the active agents provides rapid onset of the desired effects followed by sustained release from the polymeric salt.

Antineoplastics such as ifosfamide, cytoxan, carboplatin, cis-platin, leuprolide, doxorubicin, carmustine, bleomycin, and fluorouracil can be formulated in inorganic-

biopolymer complexes for regional chemotherapy. In situations in which locally disseminated tumor is discovered and surgical removal is deemed inadvisable, administration of inorganic-biopolymer complex via injection is advantageous. Charged agents can be employed as salts with medicinal complexing agents as well as free. Neutral molecules can be formulated with cyclodextrins and emulsifiers. Also, following resection, antineoplastic inorganic-biopolymer complexes can be placed in the void left by the tumor as a preventative of recurrence.

Radiopaque inorganic-biopolymer complexes can be produced by inclusion of BaSO₄, iodipamide, or other imaging agents in the complex. These formulations can be readily visualized radiographically during and after surgical procedures.

Pre-formed beads and tablets can be used as prophylactic anti-infectives and as pain control agents. These inorganic-biopolymer complexes are especially useful at the conclusion of orthopedic procedures such as joint arthroscopy and arthroplasty.

B. Medicinal Proteins

As used herein, the term "medicinal" includes proteins as well as small molecules. The term "protein" includes naturally occurring proteins, recombinant proteins, protein derivatives, chemically synthesized proteins, and synthetic peptides. Medicinal proteins useful in the subject invention include colony stimulating factors (CSF) including G-CSF, GM-CSF, and M-CSF; erythropoietin; interleukins, IL-2, IL-4, IL-6, etc; interferons; growth factors (GF) including epidermal-GF, nerve-GF; tumor necrosis factor (TNF); hormones/bioactive peptides; ACTH; angiotensin, atrial natriuretic peptides, bradykinin, dynorphins/endorphins/ β -lipotropin fragments, enkephalin; gastrointestinal peptides including gastrin and glucagon; growth hormone and growth hormone releasing factors; luteinizing hormone and releasing hormone; melanocyte stimulating hormone; neurotensin; opiate peptides; oxytocin, vasopressin and vasotocin; somatostatin; substance P; clotting factors such as Factor VIII; thrombolytic factors such as TPA and streptokinase; enzymes used for "replacement therapy," e.g., glucocerebrosidase, hexosaminidase A; and antigens used in preventative and therapeutic vaccines such as tetanus toxoid and diphtheria toxoid. Medicinal proteins of special interest appear below:

<u>Medicinal</u>	<u>Clinical Indication</u>
G-CSF	Adjunct to myelosuppressive chemotherapy
Erythropoietin	Anemia, kidney disease
"Replacement" enzymes	Heritable genetic deficiencies of enzymes
Hormones	endocrine gland failure, treatment of hormone sensitive cancers, contraception, growth promotion
Cytokines such as colony stimulating factors, e.g., GM-CSF, interferons, e.g., IFN-alpha, IFN-beta, interleukins, e.g., IL-1, IL-2 and IL-6 and TNF	Immunoadjuvants
Vaccine antigens	Immunization-preventative and therapeutic
BMP-2	Bone replacement
Wound healing promoters	burns, trauma
rh-Lysozyme	antimicrobial
Growth Factors	growth promotion
Inhibitors/antagonists of the above	

V. Non-medical Applications

There are agricultural and industrial applications of the matrices of the invention. The polymers are not necessarily of biological origin. For example, the matrix polymer can be selected from the following: polyethyleneglycol, polyvinylpyrrolidone, polyvinylalcohol, starch, xanthan, cellulose and cellulose derivatives (e.g., carboxymethylcellulose). Examples of non-ionic complexing agents include polyoxyethylene esters and ethers, and surfactants of either biological or non-biological origin. Examples of ionic complexing agents include polyacrylic acid, alginic acid, dextran sulfate, polyvinylpyridine, polyvinylamine, polyethyleneimine as well as synthetic lipid compounds.

Examples of bioactive compounds which can be used with the matrix of the invention include sterilants, pheromones, herbicides, pesticides, insecticides, fungicides, algicides, growth regulators, nematocides, repellents, and nutrients.

* * * * *

The following Examples are illustrative, but not limiting of the compositions and methods of the present invention. Other suitable modifications and adaptations of a variety of conditions and parameters normally encountered which are obvious to those skilled in the art are within the spirit and scope of this invention.

EXAMPLES

Example 1

Preparation of a radiopaque norfloxacin-inorganic-biopolymer complex

$\text{CaSO}_4 \cdot 1/2\text{H}_2\text{O}$ is sterilized by heating at 120°C for 4 hours and then divided into 1g aliquots which are stored in individual plastic containers in a desiccator. Calcium sulfate(1g), 50mg norfloxacin, and 110mg iodipamide, all finely ground, are mixed thoroughly. To this mixture is added 0.6ml of cold hyaluronic acid solution (2%). The slurry is mixed to an even consistency and is loaded into the barrel of a 3ml syringe with a

spatula. The plunger is replaced and the air expelled. The needle is attached to the syringe and the inorganic-biopolymer complex is ready for administration or casting in a mold.

Example 2

Preparation of Lidocaine Matrix

Calcium sulfate-hemihydrate (1g) was mixed with finely ground dextran (clinical grade, 0.2g) and lidocaine (.1g). The solid mixture was then stirred with 0.6 ml of water or alternatively 0.6 ml of HA (2%). The slurry was apportioned into screw-cap vials, 0.2 ml each. After 24 hr. at room temperature, the samples were refrigerated. The release experiments were done at 37°C using 1ml of buffer per vial with changes at 24 hr. intervals. The release buffer was PBS containing 0.1% sodium azide. The concentration of lidocaine was determined spectrophotometrically (260nm). See Table 3 below

TABLE 3

Release of Lidocaine for Matrices with (B) and without (A) the Matrix Biopolymer.

Matrix A		Matrix B (11% Dextran)	
Day	% Release	Day	% Release
1	85	1	24
2	10	2	26
3	1	3	22
4	1	4	15
5	1	5	6

Example 3

Preparation of an inorganic-biopolymer complex containing bound and free amikacin

Chondroitin sulfate solution (sodium salt, 5%) is converted to the acid form by passage over a column of Dowex-50. Assuming a residue molecular weight of 500, a stoichiometric amount of amikacin free base is added at 0-4°C. The pH is adjusted to 7 and the product is frozen. Alternatively, the product is freeze-dried and stored in a desiccator. Using chondroitin sulfate as the medicinal complexing agent, other complexes can be made by this procedure. Lidocaine, morphine, gentamicin, clindamycin, and doxorubicin are examples.

Calcium sulfate (1g) is thoroughly mixed with 50mg of chondroitin sulfate-amikacin (above) and 25 mg amikacin sulfate(1:2). Hyaluronic acid solution (0.6ml, 2%) is added and the mixture handled as described in Example 1.

Example 4

Preparation of cis-platin beads

Calcium sulfate (1g) is mixed with 50mg of finely ground cis-platin (cis-diaminedichloroplatinum). To this mixture 0.6ml of hyaluronic acid solution (2%) is added and the slurry is transferred to a 3ml syringe as described in Example 1. Using a 20-gauge blunt end needle, the inorganic-biopolymer complex is injected into a teflon mold with spherical holes which are 3.2 mm in diameter. After 48 hours at room temperature, the mold is split and the beads are removed with a dental explorer under sterile conditions. Beads are placed in slits made surgically around a tumor or around the site of tumor removal in an effort to prevent recurrence.

Example 5

Preparation of cefazolin-inorganic-biopolymer complex

Polymyxin sulfate solution (10%) is cooled to 0-4°C. A stoichiometric amount of barium hydroxide solution is added to produce the free base of polymyxin and insoluble barium sulfate. Four equivalents of cefazolin, dissolved in 50% THF, are added. After trituration, the suspension is filtered to remove the barium sulfate. The residue is washed to recover all of the conjugate. The solvent of the combined filtrate and washing is evaporated and the polymyxin-cefazolin salt is used as the solid. Calcium sulfate (1g) is mixed with 100mg of polymyxin-cefazolin salt and 50mg of cefazolin-sodium. To this solid mixture is added 0.6ml of hyaluronic acid (2%). The slurry is administered directly or placed in a bead or tablet mold. Other basic polypeptides, or aminoglycosides may be used in place of polymyxin.

Example 6

Penicillin G- inorganic-biopolymer complex

Penicillin G is employed simultaneously as the salt of potassium, procaine, benzathine, and polymyxin. To 2g of calcium sulfate is added 100mg of penicillin G-potassium plus 100mg procaine-penicillin and 50mg each of polymyxin-penicillin and amikacin-penicillin. After thorough mixing, 1.2 ml of 20% dextran is added and the slurry handled as described above.

Example 7

An anti-inflammatory inorganic-biopolymer complex

An apolar medicinal complexing agent such as Polysorb 80 is employed with the following forms of hydrocortisone:

A = hydrocortisone hemisuccinate-sodium

B = hydrocortisone

C = hydrocortisone acetate

D = hydrocortisone octanoate

To 1g of calcium sulfate is added 25mg each of A, B, C, and D above. To this mixture is added 0.6ml of 20% dextran plus 100ul of Polysorb 80. The slurry is handled as described above.

Example 8

Herbicide (dinoseb) inorganic-polymer composite

Dinoseb is conjugated with polyethyleneimine (PEI) using water as a solvent. To 1ml of a PEI solution (10%) is added 200mg of dinoseb and the pH is adjusted to near neutrality. This mixture (600mg) is combined with 1g of calcium sulfate and the slurry used to produce beads with a water-immiscible medium such as sesame oil. Naphthalene acetic acid can be used in place of dinoseb to produce a long-lasting root growth stimulator.

Example 9

Treatment of a bone infection

A colt, aged three months, sustained a fracture which was successfully treated surgically to the point at which an infection (Enterobacter) occurred. A matrix including norfloxacin (formulation A of Table 1) was used to treat the infection. After thorough debridement of the cavity, the void was filled with freshly prepared matrix. No surgical intervention was necessary after the treatment. The infection was eradicated and no sign of lameness appeared after 1 month.

Example 10**Preparation of the salt, amikacin-chondroitin sulfate**

Chondroitin sulfate (1g) is dissolved in 4 ml distilled water at 0-4°C TCA (1 ml ml, 32%) at 0°C is added with stirring. The solution is poured into 20 ml of cold ethanol; the precipitate is collected on a filter, washed and dried. One equivalent of solid amikacin (free base) is added. The solution is adjusted to pH 7.4. It can be used as is or supplemented with amikacin sulfate.

Example 11**Preparation of silver sulfadiazine cream - a topical anti-infective**

Component A—520g of PEG 400 plus 200g PEG 3350 warmed to form a single phase (40-50°).

Component B— 60g of PVP K-30 dissolved in 170 ml of anhydrous isopropanol

Component C – 20g of silver sulfadiazine (micronized) suspended in 30ml of anhydrous isopropanol

Preparation: Components A, B, and C are mixed with stirring at 45-55°. To this suspension 1kg of calcium sulfate hemihydrate is gradually added with stirring. After mixing is complete, the product is transferred to a polypropylene vessel and stored at room temperature or below. The product is protected from light. Viscosity can be reduced by increasing the relative amount of PEG 400 with regard to PEG 3350. The converse is also true. The weight of calcium sulfate can be reduced by 50% with the other component weights held constant. The product is then packaged into 32 ml syringes with nozzle end caps and polyethylene seals.

Use: Silver sulfadiazine cream is indicated for treatment of equine thrush and white line disease. After removal of foreign matter and necrotic tissue, silver sulfadiazine cream is applied to the hoof with concentration on the cleft of the frog. For best results

the syringe is used at 70-90°. The product is particularly advantageous for prophylactic use under shoes or pads at each shoeing.

Example 12

Silver Sulfadiazine Paste - a topical anti-infective for equine hoof rebuilding

Component A - Silver sulfadiazine cream (above)

Component B - 2% Hydroxypropyl methylcellulose in 50 % alcohol (e.g., methanol, ethanol, propanol, isopropanol)

Preparation: At 30-40° two parts of Component A are mixed with one part Component B to form a thick paste. This product is stored in closed polypropylene tubs and protected from light.

Use: Following hoof resection silver sulfadiazine paste is applied with a spatula to fill voids and reshape the hoof. It can be used under unmedicated plastic hoof rebuilders.

Example 13

Silver sulfadiazine beads - a topical anti-infective

Preparation: 1g of calcium sulfate-hemihydrate and 75 mg of silver sulfadiazine (USP, micronized) are thoroughly mixed. A slurry is made with 0.5 ml of Solution D. The solid which forms is ground to a powder; Particle size of <50 microns works well. Solution D is 10% dextran sulfate (sodium form, USP, MW=8,000) which is sterile filtered.

Use: These beads can be used directly on open wounds. Incorporation in a non-aqueous organic ointment base is useful; white petrolatum is a good choice as is polyethylene glycol based preparations. Suspension of these beads in propylene glycol or other liquid vehicle is valuable for treatment of *Otitis Externa*.

Example 14**Silver sulphadiazine film - a topical anti-infective**

The films are cast using 2% HPMC in 50% alcohol. The silver sulfadiazine beads (1-5% by wt.) described above are dispersed into the HPMC solution and the dispersion is poured onto a glass or plastic surface. Solvent evaporation results in a very strong film. Other film forming technologies are also applicable. These films can be incorporated into wound dressings and bandages. The film is stable in air but dissolves when in contact with water or moist tissue. Once in contact with moisture the microbeads begin releasing silver sulfadiazine, which is active against a broad spectrum of bacteria, yeast, and fungi.

Example 15**Porous Orthopedic Filler**

This preparation can be used to fill extraction sockets, periodontal defects, orthopedic defects, root canals, and screw channels following fracture repair, etc. Porosity allows the penetration of cells such as osteocytes. Bioactive agents such as anti-infectives and osteogenic compounds can be included to promote bone resorption in a sterile environment as the matrix is resorbed.

Component A = $\text{Ca}(\text{H}_2\text{PO}_4)_2/\text{NaHCO}_3$ (1/1)

Component B = Calcium sulfate-hemihydrate

Component C = Biopolymer solution, e.g., Solution D from Example 13

Component A (0.1-0.3g) and Component B (0.7-0.9) are thoroughly mixed (total=1 g). This solid mixture is then blended with 0.6ml of biopolymer solution. The slurry is immediately injected and allowed to solidify *in situ*. Amikacin sulfate (50-100mg) can be included as the antibiotic.

Example 16**Preparation of Sterile Amikacin Matrix**

Calcium sulfate-hemihydrate is sterilized by dry heat—120° for 4 hrs. Solution A is prepared as follows. Dextran sulfate (1g/CAS9011-18-1) is dissolved in 10 ml of water along with 3 g of amikacin sulfate (CAS 39831-55-5). The solution is filtered (0.2 micron filter) into sterile serum cap vials. To 1g of calcium sulfate-hemihydrate is added 0.5-0.7 ml of Solution A. The components are mixed thoroughly to produce a uniform slurry. The slurry can be injected directly into the patient, injected into a mold, or used to produce microbeads. Operations including mixing and beyond are conducted in a sterile space. Molds for 3-mm beads are sterilized by ethylene oxide treatment. Milling equipment is sterilized by autoclaving or by treatment with ethylene oxide.

Example 17**Treatment of equine joint sepsis**

Infection of the equine joint is characterized by heat, swelling, pain on palpation/flexion, and lameness. The use of amikacin beads is preceded by through-and-through lavage or other joint drainage/flushing technique. Amikacin beads are suspended in lactated Ringer's solution and injected, i.e., with an 18ga needle. Dosages range from 100-500mg. Systemic antibiotics may be used as an adjunct. Culture to show susceptibility is obviously desirable. If amikacin beads are not indicated, cefazolin matrix beads may be employed. Larger beads, 3mm, can be placed within the joint capsule using the arthroscope or a cannula.

Representative results with amikacin beads (100mg) are as follows:

Case 1. Luxated LR fetlock with exposure of distal M3. Prior treatment consisting of extensive joint flushing, and systemic antibiotic treatment was unsuccessful—persistent positive cultures for Staph. and Strep. Injection of 100mg of amikacin beads resulted in resolution of the infected condition—no more flaring, heat, or positive cultures. Horse returned to sound condition.

Case 2. Puncture wound of the RR fetlock resulted in sepsis of the tendon sheath. Surgery including annular resection systemic antibiotic therapy did not result in correcting the condition. Amikacin beads were injected and infection (Staph.) was eradicated as judged by culture and symptoms. Horse returned to sound condition.

Case 3. Puncture wound of left hock joint resulting in an infection. Horse was treated immediately with amikacin microbeads and the treatment repeated after one week. Infection was resolved; horse returned to training.

* * * * *

It will be readily apparent to those skilled in the art that numerous modifications and additions may be made to both the present invention, the disclosed device, and the related system without departing from the invention disclosed.

What is Claimed

1. A delivery system comprising:
 - a) an inorganic compound capable of undergoing hydration and/or crystalization, and
 - b) a matrix polymer, and/or
 - c) a complexing agent.
2. A system as in claim 1, wherein said inorganic compound is calcium sulfate.
3. A system as in claim 1, wherein said matrix polymer is a biopolymer selected from the group consisting of hyaluronic acid, chondroitin sulfate, dextran, and protein.
4. A system as in claim 1, wherein said complexing agent is selected from the group consisting of chondroitin sulfate, polyglutamic acid, polyaspartic acid, polynucleotides, a cationic polypeptide, cyclodextrin, polyoxyethylene alcohol, ester or ether, and defatted albumin.
5. A system as in claim 4, wherein said polyoxyethylene alcohol, ester or ether is a surfactant.
6. A system as in claim 4, wherein said cyclodextrin is hydroxypropyl beta cyclodextrin.
7. A system as in claim 1, wherein said complexing agent is a lipid or a liposome.
8. A system as in claim 7, wherein said lipid is a lipid of biological origin selected from the group consisting of cholesterol and lecithin.
9. A system as in claim 2, comprising calcium sulfate and a glycosaminoglycan.

10. A system as in claim 9, wherein said glycosaminoglycan is hyaluronic acid or chondroitin sulfate.

11. A system as in claim 1, wherein said system is in the form of a bead, a wafer, a tablet, a sphere, a granule or a cylinder.

12. A system as in claim 1, wherein said complexing agent is apolar.

13. A system as in claim 1, wherein said complexing agent is two or more complexing agents of more than one size.

14. A system as in claim 13, wherein said two or more complexing agents are selected from the group consisting of procaine, benzathin, polymyxin, and a polymer of cationic amino acids.

15. A system as in claim 13 wherein said two or more complexing agents are chondroitin sulfate fragments of more than one size.

16. A system as in claim 1 comprising calcium sulfate and hyaluronic acid.

17. A system as in claim 1, further comprising a medicinal.

18. A system as in claim 17 wherein said medicinal is a salt.

19. A system as in claim 17, wherein said medicinal is at least two medicinals of varying apolar character.

20. A system as in claim 19, wherein said medicinal is a series of bioactive compounds of more than one apolar character.

21. A system as in claim 20, wherein said series comprises hydrocortisone - succinate, hydrocortisone, hydrocortisone acetate and hydrocortisone octanoate.

22. A system as in claim 17, wherein said medicinal is a drug precursor.

23. A system as in claim 17, wherein said medicinal is a protein medicinal.

24. A system as in claim 1 further comprising an antiinfective selected from the group consisting of gentamicin, clarithromycin, minocycline and lincomycin, amikacin, penicillin, cefazolin, ciprofloxacin, enrofloxacin, norfloxacin, silver sulfadiazine, imipenem, piperacillin, nafcillin, cephalixin, vancomycin, nystatin, and amphotericin B or salts thereof.

25. A system as in claim 24 further comprising a chondroprotective agent.

26. A system as in claim 1, further comprising an antibiotic.

27. A system as in claim 26, wherein said antibiotic is imipenem.

28. A system as in claim 1, further comprising a bone morphogenic protein.

29. A system as in claim 1, further comprising an antineoplastic agent.

30. A system as in claim 1, further comprising an anesthetic.

31. A system as in claim 30, wherein said anesthetic is lidocaine.

32. A system as in claim 1, further comprising a radiopaque or imaging substance.

33. A system as in claim 1, further comprising a non-medicinal compound.

34. A system as in claim 33 wherein said non-medicinal compound is selected from the group consisting of a sterilant, a pheromone, a herbicide, a pesticide, an insecticide, a fungicide, an algicide, a growth regulator, a nematocide, a repellent, and a nutrient.

35. A system as in claim 1, further comprising a herbicide.

36. A system as in claim 33, wherein said matrix polymer is selected from the group consisting of polyethyleneglycol, polyvinylpyrrolidone, polyvinylalcohol, starch, xanthan, cellulose and a cellulose derivative.

37. A system as in claim 33, wherein said complexing agent is a complexing agent selected from the group consisting of a polyoxyethylene ester or ether, and a surfactant of either biological or non-biological origin.

38. A system as in claim 33, wherein said complexing agent is selected from the group consisting of polyacrylic acid, alginic acid, dextran sulfate, polyvinylpyridine, polyvinylamine, polyethyleneimine and a lipid.

39. A system as in claim 1 wherein said system is porous.

40. A system as in claim 2 further comprising dextran sulfate.

41. A system as in claim 2 further comprising polyethyleneglycol.

42. A system as in claim 40 or 41 further comprising amikacin.

43. A system as in claim 40 or 41 further comprising silver sulfadiazine.

44. A system comprising a complexing agent and a medicinal.

45. A system as in claim 44, wherein said medicinal is in the form of a salt.
46. A system as in claim 45, wherein said medicinal is anionic.
47. A system as in claim 45, wherein said medicinal is cationic.
48. A system as in claim 44, wherein said complexing agent is apolar.
49. A system as in claim 44, wherein said complexing agent is selected from the group consisting of chondroitin sulfate and a cationic polypeptide.
50. A system as in claim 44, wherein said complexing agent is selected from the group consisting of chondroitin sulfate, polyglutamic acid, polyaspartic acid, a polynucleotide, a cationic polypeptide, a carboxylic acid, cyclodextrin, a polyoxyethylene ester or ether, and defatted albumin.
51. A system as in claim 44, wherein said medicinal is an antibiotic salt selected from the group consisting of gentamicin, clarithromycin, minocycline and lincomycin, amikacin, penicillin, cefazolin, ciprofloxacin, enrofloxacin, norfloxacin, silver sulfadiazine and imipenem.
52. A system as in claim 44, wherein said medicinal is an anesthetic selected from the group consisting of lidocaine, buvicaine, morphine and hydromorphone, bupivacaine, chloroprocaine, procaine, etidocaine, prilocaine, dezocine, hydromorphone.
53. A system as in claim 44, wherein said complexing agent is chondroitin sulfate.
54. A system as in claim 46, further comprising hyaluronic acid.

55. A system as in claim 44 wherein said medicinal is an antibiotic.
56. A system as in claim 55 wherein said antibiotic is amikacin.
57. A system as in claim 53, wherein said chondroitin sulfate is an enzymatic digest composed of fragments of more than one size.
58. A system as in claim 44 wherein said complexing agent is a carboxylic acid.
59. A system as in claim 44 wherein said complexing agent is selected from the group consisting of caprylic acid, undecylenic acid, piperacillin, penicillin V, nafcillin or cefazolin.
60. A method of producing sustained release of a medicinal in a mammal comprising administering the system of claim 1 and a medicinal to said mammal.
61. A method as in claim 60, wherein said administration is by subcutaneous injection.
62. A method of treating infection in a mammal comprising administering a composition comprising the system of claim 1 and an antiinfective to said mammal.
63. A method as in claim 62, wherein said antiinfective is selected from the group consisting of gentamicin, clarithromycin, minocycline and lincomycin, amikacin, penicillin, cefazolin, ciprofloxacin, enrofloxacin, norfloxacin, silver sulfadiazine, imipenem, piperacillin, nafcillin, cephalexin, vancomycin, nystatin, and amphotericin B or salts thereof.
64. A method of diagnosing disease in a mammal comprising administering a radiopaque matrix to said mammal.

65. A method of producing a delivery system comprising mixing
(a) an inorganic compound, (b) a bioactive substance and (c) a matrix biopolymer.
66. A method as in claim 65, wherein said inorganic compound and bioactive substance are premixed and then added to said matrix biopolymer.
67. A method of scaffolding bone or filling a defect in bone comprising administering to said bone the delivery system of claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/19528**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : A61K 9/00, 9/36

US CL : 514/777

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/777, 55, 947, 953; 536/55.2; 604/892.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94/12152 A1 (PFIZER INC.) 13 October 1993, see pages 2-11.	1,2,9-11,16, 39-43
X	US 5,385,887 A (YIM et al) 31 January 1995, see col.1- col.4.	1,2, 11
X	EP 642 785 A2 (EDWARD MENDELL CO., INC.) 15 March 1995, see pages 1-6.	1,2,11
Y	US 4,946,870 A (PARTAIN et al) 07 August 1990, see col. 1-4, 7.	1,2,9, 10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

25 JANUARY 1999

Date of mailing of the international search report

10 FEB 1999

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/19528

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1,2,9-11,16,39-43

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/19528

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

The inventions listed as Groups 1-37 do not relate to a single inventive concept under PCT rule 13.1 because, under PCT rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking the inventions of groups 1-37 appears to be that they all relate to a delivery system comprising a matrix polymer, complexing agent and inorganic compound.

However, WO 94/12152 A1(PFIZER INC.) teaches the use of delivery systems composed of a variety of inorganic compounds, matrix polymers and complexing agents such as cellulose, cellulose derivatives, polyvinylalcohol, lipids, polyethylenes, polyvinylpyrrolidone, etc. (see whole document).

Therefore the technical feature linking the inventions of groups 1-37 does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

In the absence of any response from the applicant, this Authority will establish the International Preliminary Examination Report based on the main invention. The claims drawn to the main invention are as follows:

Claims 1, 2, 9-11, 16, 39-43